REMARKS

In paragraph 9 of the Office Action, the Examiner rejected Claims 13-17, 23, 24, and 28 as being unpatentable under 35 U.S.C. § 103 by Babbitt et al., U.S. Patent No. 5,766,920 ("the Babbitt '920 Patent") in view of Berd, U.S. Patent No. 5,290,551 ("the Berd '551 Patent"). The Examiner states that the Babbitt '920 Patent teaches a process of taking PMBC and contacting them with anti-CD3 of immunoreactive cells and the further exposing the cells to an immune stimulant with IL-2 to yield a population of immunoreactive cells. The Examiner states that the Berd '551 Patent teaches a vaccine comprised of irradiated tumor cells in a BCG adjuvant. According to the Examiner, it would be obvious to combine the Babbitt '920 Patent and the Berd '551 Patent to arrive at the claimed invention because both are directed to the treatment of cancer. In paragraph 10, the Examiner further argues that the teachings of multiple body sites, number of cells, and time of vaccination is obvious.

In response, Applicant has amended independent Claim 13 to recite that the vaccine is comprised of GM-CSF. Applicant respectfully notes that the claimed invention as amended neither taught or suggested by the cited prior art. The Berd '551 Patent uses BCG as the adjuvant. In addition, the Babbitt '920 Patent only uses GM-CSF as a nonspecific autologous lymphocyte activator of the cultured cells, not as an adjuvant for the vaccine. Because this limitation is neither taught or suggested by the cited references, Applicant respectfully submits that the claimed invention is patentable in view of the prior art.

Applicant has also submitted several new dependent claims. For example, Claim 30 requires that the adjuvant be GM-CSF, that the removal step be performed by leukapheresis, and the differentiation step is performed using anti-CD3. It is respectfully submitted that these claims are also not taught or suggested by the prior art.

To support the non-obviousness of the claimed invention, it is important to note that in contrast to the prior art strategies, the claimed invention of the present invention shows unexpected results. In the present invention, examples included grade III and IV malignant astrocytoma and stage IV (metastatic) renal cell carcinoma. Those cancers were selected because they are widely regarded as being untreatable regardless of what treatment strategy, immunologic or non-immunologic, is applied. Applicant has submitted a Declaration Under Section 1.32 to further demonstrate the unexpected results of the present invention.

a. Astrocytoma (brain cancer)

On the human side, the clinical trial paradigm dictates that phase I/II trials are performed with patients who have failed conventional therapy, regardless of how ineffective that therapy might be. In general, the chance of seeing a clinical effect against human grade III and IV astrocytomas already is low at the time of diagnosis, because malignant brain cancers are virtually untreatable. The probability of seeing a clinical effect in the trials of the present invention is further reduced because the trials were limited to patients whose cancers had grown back after initial surgery, radiation and chemotherapy. In short, because all treated patients had recurrent brain malignancy, documenting any clinical effect in this patient population could be regarded as evidence for unexpected results.

As shown in Table 5 of the Applicant's specification (paragraph [0104]), when using the present invention, the combined autologous cancer cell / GM-CSF vaccination with infusion of anti-CD3/IL-2 activated blood T cells shows unexpected results. Two of ten patients had complete regressions of their cancers and the survival of those two patients was greatly prolonged. The regressions are documented in before and after treatment radiological pictures of the cancers. See FIGs. 1, 2 and 3 of Declaration. Those effects are unprecedented in the annals

of brain cancer treatment, and, by themselves, could be considered as evidence of unexpected results.

Since the filing of Applicant's application, further testing has been done in accordance with the present invention. In this regard, Applicant is attaching a copy of Sloan et al., *Adoptive immunotherapy in patients with recurrent malignant glioma: preliminary results of using autologous whole-tumor vaccine plus granulocyte-macrophage colony-stimulating factor and adoptive transfer of anti-CD30-activated lymphocytes*, Neruosur. Focus, Vol. 9 (Dec. 2002) (see Exhibit A). As shown in Table 2, 9 of the 19 patients remained alive. More than 50% of the patients' cancers stopped growing for varying periods of time. Again, these effects are unprecedented and provided evidence of unexpected results and/or synergy.

b. Renal cell carcinoma studies

Human renal cell carcinoma clinical trials were performed with patients who had advanced stage IV (metastatic) renal cell carcinoma. Stage IV renal cell carcinoma is generally regarded as being untreatable. Nearly all patients diagnosed with stage IV renal cell carcinoma die from their disease, and surgery, radiation and chemotherapy have little effect on outcome. This creates a situation similar to that with brain cancer. Any clinical effect in this group of patients would be directly attributable to the treatment.

Unpublished renal cell cancer data demonstrated that combining autologous cancer cell/GM-CSF vaccination with adoptive transfer of anti-CD3/IL-2 produced unexpected results. As shown in Table 1, a 70% response rate (regression combined with >6 months progression free survival) was obtained in the study. Radiological documentation of one of the complete responses is shown in FIG. 4 of the Declaration. The patient's cancer completely disappeared in the same way that it was documented for brain cancer patients. All of the patients in whom a response was observed had significantly prolonged survival. The overall effects were similar to

the brain cancer in that complete regressions were produced and survival was prolonged in a significant proportion of treated patients. The effects were far greater than have been observed with any other treatment for metastatic renal cell carcinoma.

In summary, the clinical effects of combining autologous cancer cell / GM-CSF vaccination with adoptive transfer of anti-CD3/IL-2 stimulated effector T cells are unexpected. As such, Applicant respectfully submits Claim 13 and all claims depending therefrom are not rendered obvious by the prior art. Applicant therefore respectfully requests that the Examiner withdraw the rejection under Section 103.

II. CONCLUSION

In view of the present amendments to Applicant's claims and corresponding remarks contained herein, reconsideration and allowance of the application by the Examiner is requested. Applicant submits that the independent claims and the claims depending therefrom are patentable over the art cited by the Examiner and are in condition for allowance, which action is hereby respectfully requested. The art applied by the Examiner has been reviewed by Applicant and is believed not to anticipate or render obvious any claims in the application.

Respectfully submitted,

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